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(71) *Sökande* *Bioglan AB, Malmö SE*
Applicant (s)

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Evy Morin

Evy Morin

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PATENT- OCH REGISTRERINGSVERKET
SWEDEN

Postadress/Adress
Box 5055
S-102 42 STOCKHOLM

Telefon/Phone
+46 8 782 25 00
Vx 08-782 25 00

Telex
17978
PATOREG S

Telefax
+46 8 666 02 86
08-666 02 86

BIOLOGICALLY ACTIVE COMPOSITION

Technical Field

The present invention relates to a biologically active composition from which one or more biologically active components are to be released. More specifically, the invention relates to a biologically active composition wherein the biologically active agent is present in a supersaturated state within a carrier without being precipitated therefrom.

Background of the Invention

From *inter alia* toxicological points of view, it is often preferred, upon treatment of diseases or symptoms thereof, to deliver drugs directly to their site(s) of action. It is well known that the risks of obtaining detrimental effects of systemic origin are often markedly reduced if a drug is delivered directly to its site(s) of action. Furthermore, systemic delivery often involves metabolism of the drug prior to its appearance at the site of action, which leads to a subsequent reduction of its biological effect. Another important aspect is that in *e.g.* cases of imminent overdosage, allergic reactions or administration of contraindicating drugs, it is easy to remove topical compositions in contrast to drugs administered per-orally or by injection.

As used herein, topical administration comprises *inter alia* dermal, sub-lingual, gingival, buccal, transdermal, nasal, vaginal and rectal administration, whereby the resulting biological effect may be local and/or systemic.

In *e.g.* dermal, nasal, vaginal, buccal or sub-lingual administration, only a very limited number of drugs are capable of permeating into the human body by themselves at a useful rate. Consequently, a lot of research has been conducted in order to investigate the

i) adverse effects on the cells of the barrier have been demonstrated, and *ii)* a reduction of the protective properties of the barrier also result in increased penetration rate for any substance, not only the drug, that is present at the site of administration. It should also be mentioned, that a majority of the known chemical penetration enhancers require some time for the onset of their action, *i.e.* display a lag time of action, since they must be established in the barrier before the actual increase in penetration rate is observed.

Thirdly, the driving force of the drug for entering the body can be changed. That is, the difference in the electrochemical potential of the drug between the drug reservoir and the body can be increased. Drug delivery systems based on this approach result in a high flux of the drug through the barrier and usually also display a reduced lag time of action.

In methods based on iontophoresis, this approach is utilised by applying an electrical potential gradient across the barrier. Obviously, these methods are mainly suitable for drugs having a net charge and are therefore much less efficient for uncharged and zwitterionic species, since the flux of the two latter species is improved mainly due to *e.g.* osmotic and electroosmotic driving forces. Iontophoresis methods also have the disadvantage that they may alter the structure of the barrier.

In another approach, the flux of a drug into the body can be enhanced by increasing the chemical potential of the drug in the carrier therefor. This is normally performed by chemical optimisation of the drug composition by adjusting the degree of saturation of the drug in said carrier. The methods based on this approach offer several advantages as compared to the previously mentioned methods, since the flux of the drug is increased in comparison with subsaturated and saturated systems. Furthermore, the properties of the barrier

itself are comparatively less affected and the lag time of initiation for the pharmacological effect is reduced. There are two particularly important aspects in this approach:

i) creation of an initial high chemical potential of the drug in the composition

ii) maintenance of a high chemical potential of the drug in the vicinity of the barrier after the application of the composition.

Therefore, it is usually desirable to prepare pharmaceutical compositions which are saturated with respect of the drug. During application, another important aspect of said composition is that the solubility and diffusion properties of the drug in the used vechicle must preclude depletion of the drug in the vicinity of the barrier. Examples of compositions used for this purpose are microemulsions and emulsions.

Another approach towards keeping the composition saturated is the use of an excess amount of drug (non-solubilised) in the carrier, whereby the drug is subsequently dissolved as it replaces the drug which has penetrated through the barrier.

Yet another approach is the use of a supersaturated composition of the drug. Here, the driving force of the drug to penetrate the barrier is higher than in the saturated composition, since the drug in a supersaturated composition has higher chemical potential in comparison with the corresponding saturated composition. For example, such compositions have been prepared according to the following means or principles: *i)* dissolving the drug at temperatures and/or pressures at which the solubility of the drug is higher as compared to those temperatures and/or pressures that are relevant for medication (W.L. Chou and S. Riegelmann, *J. Pharm. Sci.*, Vol.60, No.9, pp.1281-1302, 1971; WO 97/10812), *ii)* using solid dispersions or eutectic mixtures or solid drug particles of low degree of crystallinity or of high

energy polymorphs (W.L. Chou and S. Riegelmann, *supra*), *iii)* mixing a saturated drug solution with a non-solvent therefor, thereby performing a merely physical operation, *in situ* or prior to application, an antinucleating agent being required (US 4 940 701), *iv)* solvent evaporation to the surrounding air (Coldman *et al., J. Pharm. Sci.*, **58**, No.9 (1969), pp 1098-1102), *v)* solvent penetration into the human body, *vi)* water uptake into the composition from the human body, *vii)* pH-changes in the composition caused by H^+-uptake from the human body, or *viii)* dispersing an aqueous solution or emulsion of a drug in an aqueous dispersion of a polymer latex (Lichtenberger *et al., "Polymer films from aqueous polymer dispersions as carriers for transdermal delivery of lipophilic drugs"*, 15th Int Symp CRS:Basel 1988; Abstr 89). An important common denominator of *iv)-vii)* is that the supersaturation is not initally present in the composition, and is therefore *de facto* not accomplished until the composition is applied to a human body. Furthermore, a major problem with all the compositions *i)-viii)* is that the drug generally precipitates in a relatively short time, in which case the saturation degree becomes markedly reduced.

In DD 217 989, a subsaturated solution of a drug is mixed with a solution or suspension of an acrylate, after with the mixture so prepared is dried, whereby a supersaturated composition is obtained by use of an exclusively physical operation.

W.L. Chou and S. Riegelmann (*J. Pharm. Sci.*, Vol.58, No. 12, pp.1505-1510, 1969) have reported that in matrices of higher molecular weight polyethylene glycols, precipitation of a supersaturated drug dissolved therein is usually sluggish. In said document, supersaturation was obtained through either direct melting or solvent concentration, *i.e.* by use of typical physical operations.

In the case of biologically active compositions, the inventors know of no other relevant supersaturated compositions than those mentioned above.

As prior art, reference is also made to WO 97/00670, which discloses a composition of the type claimed herein, *viz* with a biologically active agent in a carrier comprising a glass-forming substance containing a plasticizer. However, said reference does not disclose or suggest those features of the present invention which have been found crucial to impart a stable, supersaturated state to such a composition.

General Disclosure of the Invention

A novel approach for obtaining a biologically active composition with outstanding delivery rate of its active component(s) has now been devloped, wherein said composition comprises a biologically active agent which is present in a substantially stable supersaturated state. In brief summary, it has been found that by subjecting a carrier starting substance to such chemical operation(s) that a carrier matrix of substantially non-crystalline or amorphous nature is created, in which the degree of saturation of a biologically active agent is higher than the degree of saturation of said agent in the starting carrier substance, a surprisingly stable supersaturated composition can be obtained. In the composition thus prepared, the precipitation of said agent is substantially, or completely, inhibited by said carrier matrix *per se*.

The term "biologically active agent", as used herein, also comprises such progenitors thereto which are readily transformable, *e.g.* enzymatically and/or hydrolytically, to a biologically active agent *per se*.

Thus, the present invention relates to a novel biologically active composition which comprises a biologically active agent to be released therefrom, said biologically active agent being dissolved or dispersed in

a supersaturated state within a carrier, which carrier is a liquid and/or solid substantially non-crystalline matrix, and where the precipitation of said biologically active agent is substantially, or completely, inhibited therein.

The term "liquid", as used herein, also comprises such viscous materials as creams, pastes, ointments and gels.

The present invention also relates to a method for the preparation of a biologically active composition comprising a biologically active agent dissolved or dispersed in a carrier therefor as well as use of said composition as a medicament, wherein said biologically active agent preferably is a pharmaceutically active agent.

The term "pharmaceutically active agent", as used herein, also comprises such progenitors, *e.g.* pro-drugs, which are readily transformable, *e.g.* enzymatically and/or hydrolytically, to a pharmaceutically active agent *per se*.

One of the objects of the present invention is thus to provide a supersaturated composition which does not display any significant precipitation or loss of effect during long-term storage at room temperature, or even at above or below room temperature, during *e.g.* months or even years.

Another object of the present invention is to provide a stable supersaturated composition which is easily handled and does not require professional assistance upon use thereof.

As a result of the high delivery rate of its active component(s), yet another object of the present invention is to provide a composition which allows for efficient topical treatment, preferably dermal or transdermal administration to small areas, which is a general advantage in the topical administration of drugs.

Detailed Disclosure of the Invention

More specifically, the invention refers to a biologically active composition with high delivery rate of its active component(s), said composition comprising a biologically active agent dissolved or dispersed in a carrier therefor, wherein said carrier is a liquid and/or solid substantially non-crystalline matrix and in which said biologically active agent is present in a supersaturated state and, the precipitation of said biologically active agent being substantially, or completely, inhibited by said matrix.

Generally, said liquid and/or solid substantially non-crystalline matrix is obtainable, or obtained, by subjecting one or more starting substance(s) to such chemical operation(s) that a liquid and/or solid substantially non-crystalline matrix is provided in which the degree of saturation of said biologically active agent is increased in comparison with the degree of saturation of said agent in the starting substance(s).

In one embodiment of the composition according to the present invention, said supersaturated state is obtainable by subjecting one or more carrier starting substance(s) to such chemical operation(s) that a matrix is provided in which the degree of saturation of said biologically active agent is higher than the degree of saturation of said biologically active agent in said carrier starting substance(s), the biologically active agent being added before said chemical operation(s).

In another embodiment of the invention, said supersaturated state is obtainable by subjecting one or more carrier starting substance(s) to such chemical operation(s) that a matrix is provided in which the degree of saturation of said biologically active agent is higher than the degree of saturation of said biologically active agent in said carrier starting substance(s), the biologically active agent being added at a predetermined point of time after said chemical operation(s) have been

initiated, after which the composition thus prepared is further subjected to said chemical operation(s).

Other preferable embodiments of the composition claimed will be referred to below in connection with the method.

Thus, the present invention also discloses a method for the preparation of a biologically active composition comprising a biologically active agent dissolved or dispersed in a carrier therefor, wherein

a carrier starting substance, or a mixture of two or more different starting substances, is (are) subjected to such chemical operation(s) that a liquid and/or solid non-crystalline carrier matrix is formed, in which the degree of saturation of a biologically active agent is higher than the degree of saturation of said agent in said carrier starting substance(s), said chemical operation(s) being performed either:

i) in the presence of said biologically active agent; or

ii) in the absence of said biologically active agent, after which said agent at a predetermined point of time is added and the composition thus prepared is further subjected to said chemical operation(s);

addition of said biologically active agent in both *i)* and *ii)* being made using an amount such that a supersaturated state is obtained.

In one embodiment of the invention, the degree of saturation of a biologically active agent is higher as a result of such chemical operation(s) that a liquid and/or solid non-crystalline carrier matrix is formed, in which the solubility of a biologically active agent is lower than the solubility of said agent in said carrier starting substance(s).

In another embodiment of the invention, the degree of saturation of a biologically active agent is higher as a result of such chemical operation(s) that a liquid

and/or solid non-crystalline carrier matrix is formed, in which the degree of dissociation and/or degree of protonation of a biologically active agent is different from the degree of dissociation and/or degree of protonation of said agent in said carrier starting substance(s). As a non-limiting example, this embodiment allows formation *in situ* of a suitably charged, *e.g.* protonated or deprotonated, or non-charged form of said biologically active agent, which form has a higher skin penetration rate in comparison with the form of said agent present before said chemical operation(s) is initiated.

In yet another embodiment of the invention, the degree of saturation of a biologically active agent is increased by such chemical operation(s) that both the two embodiments set forth above are practised either simultaneously or consecutively.

In one embodiment of the invention, said biologically active agent is being added, either above or around room temperature, in solid and/or liquid, *i.e.* melted, state and is subsequently dissolved in said starting substance(s) either above or around room temperature.

In another embodiment of the invention, said biologically active agent is being added, either above or around room temperature, as a solution or dispersion and is subsequently dissolved in said starting substance(s) either above or around room temperature

According to the present invention, above room temperature is a temperature of around 25-200°C, preferably around 30-150°C, more preferably around 35-100°C and most preferably around 40-80°C.

The particular addition method used for said agent can be any common inclusion technique available to a person skilled in the art, and said solution or dispersion of the biologically active agent can be

prepared *inter alia* by solvent evaporation, freeze-drying or by use of any one of the methods *i)-vii) (vide supra)*.

Preferably, in the composition according to the invention as well as in the method for preparation thereof, the starting substance(s) act(s) as solvent or dispersing medium.

Said chemical operation(s) generally involve(s) one or more chemical reactions, preferably etherifying, esterifying, substitution, addition, oligomerising and/or polymerising reactions, wherein polymerising reactions are the most preferred.

Said carrier starting substance(s), which is subsequently subjected to said operation(s) above, is selected from monomers, acids, such as mono-, di- or triacids or higher acids, alcohols, including mono-, di- or triols, ketones, aldehydes, saccharides and derivatives thereof, acrylic or acrylamide type compounds, such as methyl methacrylate, monomers of PEO-diacrylate (PEO=polyethylene oxide), cyanoacrylate, acrylate saccharides, including acrylate starch, acrylate lactate, acrylate glycolate, isocyanates, ethylene oxide, propylene oxide, pyrrolidone, PEO-diacrylate, ethylene-vinyl acetate, monomers of organic siloxanes and oligomers or prepolymers thereof. As indicated earlier, one, two or more of the above substances can be chosen, thereby allowing the formation of co-polymers and/or higher polymers.

It is to be understood by a person skilled in the art, that said chemical operation(s) is performed to such a degree of completion that a desired non-crystalline carrier matrix is obtained, which matrix is optimal for a particular biologically active agent in a particular context. Thus, all of the starting substance(s) present when said chemical operation(s) is initiated do not necessarily have to react completely in order to carry out the invention, as long as the desired degree of supersaturation is attained.

In a preferred embodiment of the present invention, the carrier starting substances are an acid and an alcohol, said formed non-crystalline matrix comprising, or being, an ester and/or polyester thereof. In a more preferred embodiment, said carrier starting substances are citric acid and propylene glycol.

In an alternative embodiment, the starting substance is one bi- or multi-functional substance only, which when subjected to said chemical operation(s) provides the desired non-crystalline carrier matrix by chemical reaction(s) with itself. In a non-limiting disclosure, such a starting substance can be citric acid, which when subjected to esterifying conditions provides a non-crystalline citric acid ester and/or polyester matrix according to the invention.

According to the present invention, suitable chemical operation(s) involve(s) subjecting said carrier starting substance(s) to such polymerising conditions which are normally used, according to standard reference literature, for the selected starting substance(s) or combinations thereof. Furthermore, such polymerising conditions should be chosen in order to optimise the manufacturing procedure, in respect of *e.g.* the stability of said agent, manufacturing time and degree of supersaturation, for the particular biologically active agent used. Typically, said conditions comprise *e.g.* subjecting said carrier starting substance(s) to a temperature from around -50°C to around 300°C, preferably around 0-150°C, more preferably around 20-100°C, even more preferably around 50-80°C and most preferably around 70°C. Said temperature ranges are particularly preferred when the starting substance(s) are a mixture of citric acid and propylene glycol. Naturally, said chemical reaction(s) are selected and performed so that in each case the maximum or optimum delivery rate of said biologically active agent is obtained.

Preferably, said chemical reaction(s) is (are) performed for a time period of from 1 minute to 6 months, preferably from 0,5 hours to 4 months, more preferably from 1 hour to 3 months and most preferably from 1 to 2 months.

The predetermined point of time (*vide supra*), as measured after said chemical operation(s) have been initiated, is generally from 1 minute to 6 months, preferably from 0,5 hours to 4 months, more preferably from 1 hour to 3 months and most preferably from 1 to 2 months, after which the composition thus obtained is further subjected to said chemical operation(s) for a time period of about from 1 minute to 6 months, preferably from 0,5 hours to 4 months, more preferably from 1 hour to 3 months and most preferably from 1 to 2 months.

The used chemical reaction(s) in the present invention preferably comprise a polymerisation reaction and most preferably such reaction in which ether or ester bonds are formed. Other preferred polymerisation reactions are step polymerisation reactions and chain polymerisation reactions comprising either radical initiation, ionic initiation or coordination complex initiation.

According to the present invention, some of the monofunctional starting substance(s) above, *e.g.* monoacids and -alcohols, can also be used to form a non-crystalline matrix consisting of *e.g.* monoesters and monoethers. Monofunctional monomers can also be introduced into said chemical reaction as a means of modifying the reaction or controlling the end point thereof.

As already indicated, in order to efficiently inhibit precipitation of the supersaturated biologically active agent, said formed matrix is of a substantially non-crystalline, or amorphous, nature. Polymers, co-polymers, oligomers and ethers or esters of the previosly

outlined starting substance(s) (*vide supra*) are particularly useful for this purpose.

As a part of the working theory which forms the basis of the disclosed invention, it is assumed that the solubility of most biologically active agents in the forming non-crystalline matrix is *lowered* during the progression of said chemical reaction, which reaction generally results in the formation of a matrix consisting of molecules with a considerably larger molecular weight than the starting substance(s). Consequently, the regulation of the molecular weight distribution of the molecules which constitute the formed non-crystalline matrix provides a means for controlling the solubility of the biologically active agent agent in said matrix. In addition, the molecular weight distribution is of importance for the diffusion rate of said agent through said matrix.

Non-limiting examples of biologically active agents, preferably pharmaceutically active agents, which are suitable for use in the present invention are *e.g.*, guanosides, corticosteroids, psychopharmaceutical hormones, oxicams, peptides, proteins as well as agents selected from the group of antibiotics, antivirals, antimicrobials, anticancer agents, antifungals, oestrogens, antiinflammatory agents, neuroleptic agents, melanocyte stimulants and gland stimulants, preferably stimulators of sebaceous and pilo-sebaceous glands, and agents with an effect on mast cell secretion.

In an alternative embodiment of the present invention, the biologically active agent may also react reversibly with said starting substance(s) in such a manner that *e.g.* esters, ethers, co-polymers and/or other conjugates are formed. Thus, this embodiment allows preparation of a non-crystalline matrix containing both said biologically active agent in a substantially stable supersaturated state and conjugate(s) thereof, whereas said conjugate(s) can be present in either a

subsaturated, saturated or supersaturated state. Alternatively, said conjugate(s) can be present in a supersaturated state, whereas said biologically active agent is present in either a subsaturated, saturated or supersaturated state. Therefore, in the case where said biologically active agent is a drug, this particular embodiment allows formation *in situ* of a corresponding drug progenitor, which may either function as a pro-drug or as a depot of the supersaturated drug, or a combination of both. As an example of this embodiment, a biologically active agent containing a carboxylic acid or alcoholic functionality may form an ester with said carrier starting substance(s) when a mixture thereof is subjected to esterifying conditions.

In another embodiment of the present invention, the starting substance(s) can be an ester and/or polyester matrix, or an ether and/or polyether matrix, to which a biologically active agent is added, after which the dispersion or solution formed is subjected to a hydrolysis reaction providing a liquid and/or solid non-crystalline carrier matrix in which the degree of saturation of said biologically active agent is higher than the degree of saturation of said biologically active agent in said starting substance(s), a stable supersaturated dispersion or solution thus being obtained. As a non-limiting example of such an embodiment, the starting substance(s) may consist of several esters and/or polyesters, of which one or several is much more readily hydrolysed in comparison with all other substances present, including the biologically active agent.

In yet another embodiment of the invention, a minor amount of said starting substance(s) is subjected to said chemical conditions, preferably a polymerisation, in the presence of a solvent, whereby a supersaturated one- or two-phase matrix is formed, such as a liquid/solid non-crystalline matrix.

However, in the most preferred embodiment, the biologically active composition consists of one liquid or solid phase only.

As earlier indicated, in another embodiment of the present invention the carrier starting substance(s) can be subjected to said chemical reaction(s), preferably a polymerisation, in advance and without the presence of said biologically active agent. By using this approach, a prefabricated liquid and/or solid non-crystalline matrix is provided, to which matrix a biologically active agent can subsequently be added at a predetermined point of time by use of any suitable inclusion method, such as *e.g.* mixing, heating, freeze-drying and/or solvent evaporation, after which the composition thus prepared is further subjected to said chemical reaction(s), which is (are) either identical or somewhat modified, by *e.g.* use of a lower reaction temperature or further addition of one or more of the previously outlined starting substance(s), in comparison with the chemical reaction(s) performed initially.

The scope of the present invention is not limited to the specific embodiments disclosed above, and the disclosed invention may optionally be combined with the methods *i)-vii)* (*vide supra*) in any suitable manner, if deemed necessary in any particular case. As a non-limiting example, the pH of the composition prepared according to the invention may optionally be subsequently modified by inclusion of a suitable acidic or basic compound, if useful in a particular context.

The following non-limiting example will illustrate the present invention further.

Brief description of the enclosed diagrams

Diagram 1 shows the amount of permeated metronidazole as a function of time for the subsaturated compositions A_0, A_1, A_2 and the saturated composition C.

Diagram 2 shows the amount of permeated metronidazole as a function of time for the subsaturated composition A_0, the saturated composition C and the supersaturated compositions B_1 and B_2.

Experimental part

The degree of supersaturation was characterised by the permeation rate of the biologically active agent through a membrane (Silastic sheeting NRV, 0,005 inches, serial #HH055353) by using a Franz diffusion cell (FDC-400 Crown Glass Company) with a cell opening area of 2,011 cm^2. All permeation rate measurements were performed at 25°C and deaerated H_2O was used as acceptor phase on the opposing side of the membrane. The donor and acceptor phase were both sealed with parafilm, and each experiment was performed in triplicate.

Example 1:

Starting substances: citric acid (CiAc) and propylene glycol

Six parts of CiAc and four parts of propylene glycol were added to a sealable container at room temperature, after which said container was sealed. The resulting mixture was stirred with a magnetic stirrer solid and the temperature was raised to and maintained at 80°C until all CiAc was dissolved, after which the solution was allowed to attain room temperature. This solution was denoted A. Solid metronidazole was then added to the solution A in a 5:95 ratio (w/w), after which the metronidazole was dissolved by magnetic stirring at room temperature. The solution thus prepared was then split into two solutions denoted A_0 and B, respectively.

As reference, a solution of 4 parts of CiAc and 6 parts of propylene glycol was prepared as above. Solid metronidazole in a 7,5:92,5 ratio (w/w) was added, and the mixture was stirred at room temperature for three days. After centrifugation resulting in sedimentation of non-dissolved metronidazole, the obtained supernatant thus consisted of a saturated metronidazole composition, denoted C. The obtained final ratio between metronidazole and CiAc/propylene glycol was 7:93 (w/w).

Due to high viscosity, the corresponding saturated composition with 6 parts of CiAc and 4 parts of propylene glycol could not be prepared in the above manner. However, it is reasonable to assume that the permeation rate of metronidazole from such a composition, could it be prepared readily, would not be significantly different from that of C.

The underlying principles behind the compositions A-C were the following:

A_0 is a *subsaturated* mixture of a pharmaceutically active agent and carrier starting substances which is not actively subjected to polymerisation;

in B, the starting substances are subjected to polymerisation conditions in the presence of a pharmaceutically active agent; and

in C, the permeation rate for a *saturated* solution of a pharmaceutically active agent in a matrix of said carrier starting substances is illustrated.

The compositions A-C were then treated as follows:

In A, the permeation rate measurements were performed directly after the manufacturing of A_0 as well as after one month (A_1) and two months (A_2).

B was split into two compositions, which were stored at 70°C for one month (B_1) and two months (B_2), respectively, after which time period the permeation rate measurements were performed on the formed compositions B_1 and B_2, respectively.

The composition C was used directly after the preparation thereof.

The measured permeation rates are depicted in the enclosed diagrams 1 and 2.

Diagram 2 shows that a considerably higher permeation rate is obtained in the compositions B_1 and B_2, as compared to any one of the compositions A or C. This is in turn indisputable evidence that the degree of saturation is significantly higher in the compositions B_1 and B_2 than in any one of the compositions A or C. Consequently, the following conclusions are supported:

A: No supersaturation is attained, and the subsaturation in respect of metronidazole is maintained during storage.

B: Supersaturation of the initially subsaturated composition is attained upon polymerisation. Further polymerisation results in an even higher permeation rate, *i.e.* higher degree of saturation, which is illustrated by B_1 and B_2.

Here, it is important to note that the *concentration* of metronidazole in all the compositions A and B is the same, but as a result of the method according to the invention, the thermodynamic potential of metronidazole in B has unexpectedly been raised to such a level that a significantly increased permeation rate of metronidzole is observed.

In summary, it is clearly realised that biologically active compositions which are prepared or obtainable in accordance with the present invention are useful as medicaments. Furthermore, the biologically active compositions according to the invention are also useful in a non-medicinal context, such as in cosmetic skin products. More specifically, said compositions should be highly efficient in dermal application to a mammal, preferably man, as well as in any general application where a biological barrier is to be penetrated by a biologically active agent.

CLAIMS

1. A biologically active composition comprising a biologically active agent to be released therefrom, said biologically active agent being dissolved or dispersed in a carrier therefor, wherein said carrier is a liquid and/or solid non-crystalline matrix in which said biologically active agent is present in a supersaturated state and in which the precipitation of said biologically active agent is substantially inhibited by said matrix.

2. A composition according to claim 1, wherein said supersaturated state is obtainable by subjecting one or more carrier starting substance(s) to such chemical operation(s) that said liquid and/or solid non-crystalline carrier matrix is provided in which the degree of saturation of said biologically active agent is higher than in said carrier starting substance(s), the biologically active agent being added before said chemical operation(s) have been completed.

3. A composition according to claim 2, wherein said higher degree of saturation is the result of such chemical operation(s) that the solubility of the biologically active agent in said matrix is lower than the solubility thereof in said carrier starting substance(s).

4. A composition according to any one of claims 2-3, wherein said higher degree of saturation is the result of such chemical operation(s) that the degree of dissociation and/or degree of protonation of the biologically active agent is different from the degree of dissociation and/or degree of protonation of said agent in said carrier starting substance(s).

5. A composition according to any one of claims 2-4, wherein said biologically active agent is added before said chemical operation(s) have been initiated.

6. A composition according to any one of claims 2-4, wherein said biologically active agent is added at a predetermined point of time after said chemical operation(s) have been initiated, the composition thus obtained then being further subjected to said chemical operation(s).

7. A composition according to claim 6, wherein said predetermined point of time is from 1 minute to 6 months, preferably from 0,5 hours to 4 months, more preferably from 1 hour to 3 months and most preferably from 1 to 2 months after said chemical operation(s) have been initiated.

8. A composition according to claim 7, wherein the composition is further subjected to said chemical operation(s) for a time period of about from 1 minute to 6 months, preferably from 0,5 hours to 4 months, more preferably from 1 hour to 3 months and most preferably from 1 to 2 months.

9. A composition according to any one of claims 2-8, wherein said starting substance(s), or said formed non-crystalline matrix, act(s) as a solvent or dispersing medium.

10. A composition according to any one of claims 2-9, wherein said biologically active agent is added as a solid and/or liquid which is subsequently dissolved in said carrier.

11. A composition according to any one of claims 2-9, wherein said biologically active agent is added in the form of a solution or dispersion.

12. A composition according to any one of claims 2-11, wherein said biologically active agent is added above or around room temperature.

13. A composition according to any one of claims 2-12, wherein said chemical operation(s) comprise one or more chemical reactions.

14. A composition according to claim 13, wherein said chemical reaction(s) comprise etherifying, esterifying, substitution, addition, oligomerising and/or polymerising reactions.

15. A composition according to claim 14, wherein said chemical reaction(s) is (are) selected and performed so as to provide optimal delivery rate of said biologically active agent.

16. A composition according to any one of claims 2-15, wherein said chemical operation(s) involve(s) subjecting said carrier starting substance(s) to a temperature of from around -50°C to around 300°C, preferably around 0-150°C, more preferably around 20-100°C, even more preferably around 50-80°C and most preferably around 70°C.

17. A composition according to any one of claims 2-16, wherein said chemical operation(s) is (are) conducted for a time period of from 1 minute to 6 months, preferably from 0,5 hours to 4 months, more preferably from 1 hour to 3 months and most preferably from 1 to 2 months.

18. A composition according to any one of claims 2-17, wherein said carrier starting substance, or mixture of two or more different carrier starting substances, is selected from monomers, acids, such as mono-, di- or triacids or higher acids, alcohols, including mono-, di- or triols, ketones, aldehydes, saccharides and derivatives thereof, acrylic or acrylamide type compounds, such as methyl methacrylate, monomers of PEO-diacrylate, cyanoacrylate, acrylate saccharides, including acrylate starch, acrylate lactate, acrylate glycolate, isocyanates, ethylene oxide, propylene oxide, pyrrolidone, PEO-diacrylate, ethylene-vinyl acetate, monomers of organic siloxanes, and oligomers or prepolymers thereof.

19. A composition according to claim 18, wherein the acid is a monomeric acid and the alcohol is a monomeric alcohol, said non-crystalline matrix comprising an ester and/or polyester thereof.

20. A composition according to claim 19, wherein said monomeric acid is citric acid.

21. A composition according to any one of claims 19 and 20, wherein said monomeric alcohol is propylene glycol.

22. A composition according to any one of the preceeding claims, which consists of one liquid or solid phase only.

23. A composition according to any one of the preceeding claims, wherein the biologically active agent is a pharmaceutically active agent.

24. A composition according to claim 23, wherein the pharmaceutically active agent is selected from the group

consisting of guanosides, corticosteroids, psychopharmaceutical hormones, oxicams, peptides, proteins, antibiotics, antivirals, antimicrobials, anticancer agents, antifungals, oestrogens, antiinflammatory agents, neuroleptic agents, melanocyte stimulants and gland stimulants, preferably stimulators of sebaceous and pilo-sebaceous glands, and agents with an effect on mast cell secretion.

25. A composition according to any one of claims 23 and 24 for use as a medicament.

26. A composition according to any one of the preceeding claims for topical, preferably dermal application to a mammal, preferably man.

27. A method for the preparation of a biologically active composition comprising a biologically active agent dissolved or dispersed in a carrier therefor, wherein a carrier starting substance, or a mixture of two or more different carrier starting substances, is (are) subjected to such chemical operation(s) that a liquid and/or solid non-crystalline carrier matrix is formed, in which the degree of saturation of said biologically active agent is higher than in said carrier starting substance(s), said biologically active agent being added before said chemical operation(s) have been completed and in an amount such that a supersaturated state is obtained.

28. A method according to claim 27, wherein said composition is as defined in any one of claims 3-26.

Abstract

The invention relates to a novel biologically active composition which comprises a biologically active agent to be released therefrom, said biologically active agent being dissolved or dispersed in a supersaturated state within a carrier, which carrier is a liquid and/or solid non-crystalline matrix, and where the precipitation of said biologically active agent is substantially, or completely, inhibited therein. Said supersaturated state is obtainable by subjecting one or more carrier starting substance(s) to such chemical operation(s) that a matrix is provided in which the degree of saturation of said biologically active agent is higher than the degree of saturation of said biologically active agent in said carrier starting substance(s), the biologically active agent being added either before said chemical operation(s) or after a predetermined point of time, after which the composition thus prepared is further subjected to said chemical operation(s).

Diagram 1

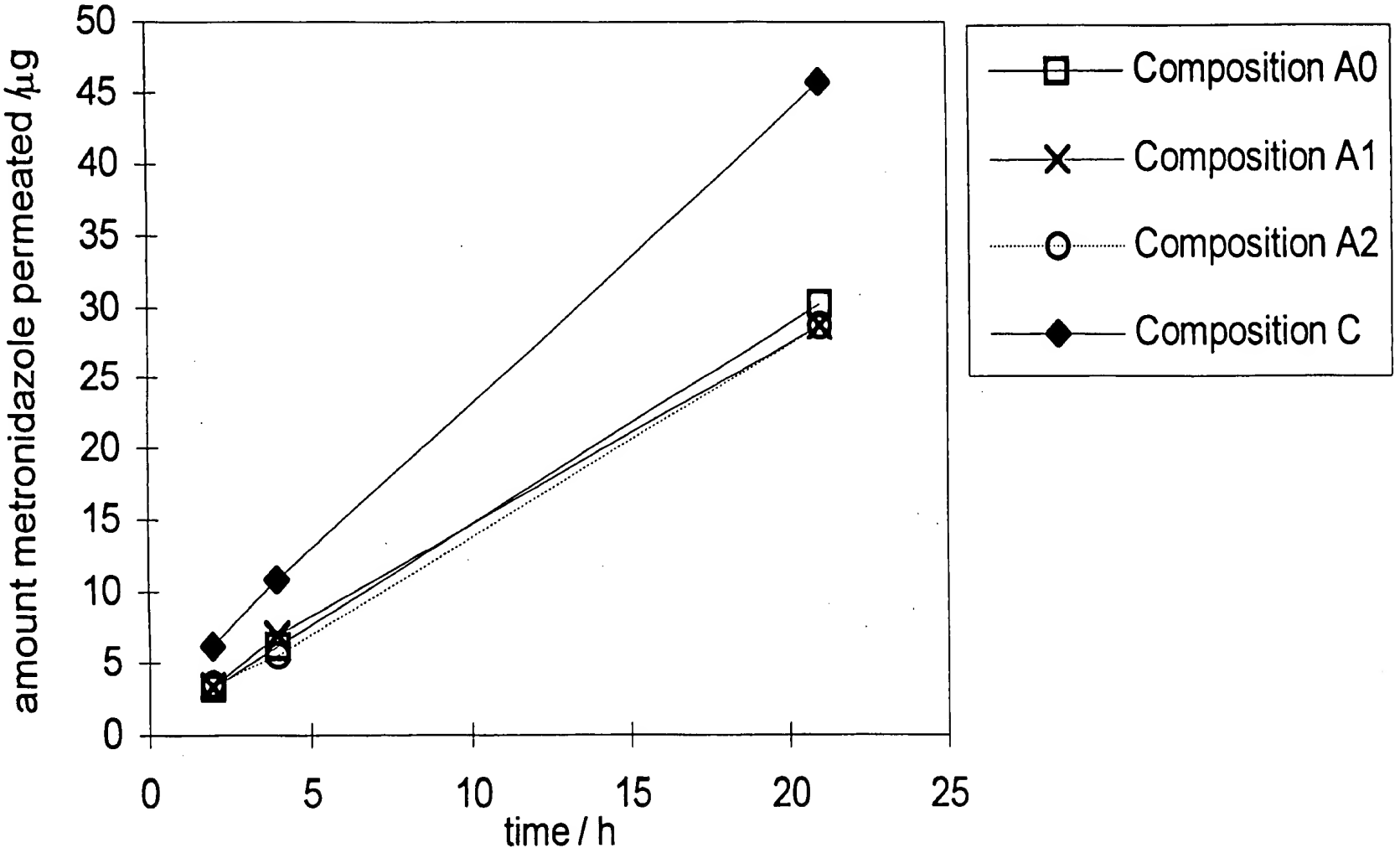
amount metronidazole permeated /µg
50
45
40
35
30
25
20
15
10
5
0
0
5
10
15
20
25
time / h
Composition A0
Composition A1
Composition A2
Composition C

Diagram 2